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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,098	09/29/2003	Upender Velaparthi	LD0314 NP	2422

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EXAMINER	
FEDOWITZ, MATTHEW L	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 08/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/674,098	VELAPARTHI ET AL.	
	Examiner	Art Unit	
	Matthew L. Fedowitz	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *9* is/are allowed.

6)☒ Claim(s) *1-4,6-8 and 10-18* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/31/04 & 6/1/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18 are pending in this action.

Allowable Subject Matter

Claim 9 is allowed. The reason the five compounds in claim 9 are allowed is because a search of the prior art does not teach or reasonably suggest the five specific compounds claimed by the applicant. Specifically, the prior art does not teach or suggest compounds where the quinoline-2-one and quinoline-4-one portions are linked to chloro-phenyl groups through 2-hydroxy-ethylamino groups.

Claim Objections

Claim 5 is objected to because it depends from a rejected base claim. However, if claim 5 were to be rewritten in independent form with all of the limitations pertaining thereto then claim 5 would be allowable. Claim 5 rewritten in independent form would be allowable because the prior art does not teach or reasonable suggest compounds wherein the R1 and R7 are H, Y is O, W is N, R3 and r5 are as defined in the claims and R6 is a compound where R6 is – NHCH2CH(OH)aryl or NHCH(CH2OH)CH2aryl.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

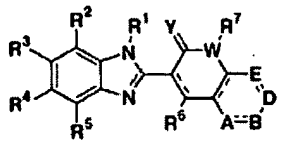
The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 6-8 and 10-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Renhowe et al. (US 2003/0028018 A1, US 6,605,617 B2 and US 2002/0103230 A1) and Fraley et al.

I. Compound and Composition Claims

Claims 1-4 and 6-8 are drawn to compounds of formulas I and II as shown below. Wherein the variables of formulas I and II are described within claim 1 and further narrowed in claims 2-4 and 6-8.



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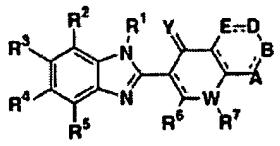


II

Claims 10-12 are drawn to compositions that contain the compounds of formulas I and II above and a pharmaceutically acceptable carrier and an anti-cancer agent.

Renhowe et al. in US 2003/0028018 A1, US 6,605,617 B2 and US 2002/0103230 A1 teach the compounds claimed by the applicant. Specifically, Renhowe et al. in US 2003/0028018

A1 teach those compounds claimed by the applicant. The substitutions for A, B, D, E, Y and W are taught throughout the reference as well as the substitutions for the R1 through R7 position (see pages 1-39). The specific substitutions for R1, R3, R5, R6, R7, Y and W as found in claims 2-4 and 6-8 are also taught (see paragraphs 241-247 and the examples found on pages 39-52). In addition, Renhowe et al. in US 2003/0028018 A1 teach pharmaceutical compositions (see paragraphs 268, 285 and claim 36). US 2003/0028018 A1 does not teach all of the combinations of compounds claimed by the applicant in formula I. US 2003/0028018 A1 also does not teach compounds of formula II.

Renhowe et al. in US 6,605,617 B2 and US 2002/0103230 A1 and Fraley et al. in US 6,479,512 B1 teach further embodiments of the applicant's claimed compounds as well as those compounds in combination with a pharmaceutically acceptable carrier as well as in combination with a an anti-cancer compound. Renhowe et al. in US 6,605,617 B2 teach those further embodiments of the applicant's claimed compounds with the substitutions as claimed by the applicant (see column 22 line 8 through column 6 line 26 and the examples in column 69 line 9 - column 93 line 45) as well as in a pharmaceutically acceptable composition (see column 57 line 62-column 61 line 5). Renhowe et al. in US 2002/0103230 A1 teach those further embodiments of the applicant's claimed compounds with the substitutions as claimed by the applicant (see paragraphs 65-224, examples 1-18 and paragraphs 264-265 and claims 1-18) as well as in a pharmaceutically acceptable composition (see paragraph 192-206). Fraley et al. in 6,479,512 B1 teach tyrosine kinase inhibitors that read on those compounds and compositions claimed by the applicant as well as in combination with an anticancer agent (see column 3 line 50 – column 10 line 67, column 53-64 and claims 1-7). JP 11321093 A assigned to Nippon Kayaku also teaches the variable W substituted with oxygen (see pages 2 and 4).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings above to obtain the compounds and compositions as claimed in the instant application. All of the moieties, which are substituted in the instant application, are taught in the art, and the locations of substitution are correlative with the locations of substitution in the art. Obviousness based on the significant similarity of structure and function entails the very motivation to make the claimed compounds and compositions in expectation that compounds similar in structure will have similar properties; therefore, one of ordinary skill in the art would be motivated to claim the compounds and compositions in searching for new tyrosine kinase inhibitors.

The applicant may obviate this rejection by amending the claims to exclude the prior art, canceling the claims or amending the claims to include a proviso wherein the compounds and compositions claimed will not be obvious over the prior art. If the applicant chooses anyone of the methods above to obviate the rejection then the applicant is encouraged to include a brief and concise explanation of how the amendments obviate the rejection from the prior art in order to expedite prosecution.

II. Method Claims

Claims 13-18 are drawn to methods of treatment claims that depend from compound formulas I and II in claim 1 and the composition of claim 10. The method of treatment claims are specifically drawn to treating a condition associated with at least one tyrosine kinase enzyme as well as proliferative diseases; wherein the condition associated with at least one tyrosine kinase enzyme can be treated in combination with an anti-cancer agent.

The teachings of Renhowe et al. in US 2003/0028018 A1, US 6,605,617 B2 and US 2002/0103230 A1 and Fraley et al. in US 6,479,512 B1 are discussed above wherein the compounds of formulas I and II are disclosed. Renhowe et al. in US 2003/0028018 A1 also teach that inhibition of angiogenesis is expected to halt the growth of cancer cells (see paragraphs 3-16); wherein the inhibition of angiogenesis achieved by administering an inhibitor of vascular endothelial growth factor receptor tyrosine kinase (see claim 37). Renhowe et al. in US 2003/0028018 A1, however, does not teach the same methods as claimed by the applicant.

Renhowe et al. in US 6,605,617 B2 and US 2002/0103230 A1 and Fraley et al. in US 6,479,512 B1 do teach the methods of treatment as claimed by the applicant. Renhowe et al. in US 6,605,617 B2 teach methods of treating a condition associated with a tyrosine kinase enzyme; the specific enzymes; wherein the condition is cancer; wherein the treatment is with a therapeutically effective and wherein proliferative diseases are treated with a composition derived the compounds claimed (see column 1 line 24-column 3 line 36, column 60 line 53-column 61 line 26 and claims 29-30). Renhowe et al. in US 2002/0103230 A1 also teach the methods listed above (see paragraph 3-15, 207-211 and claims 18-21). Fraley et al. in US 6,479,512 B1 teach the methods above as well as a method of treating cancer wherein the tyrosine kinase inhibitor is administered in combination with at least one other anti-cancer agent (see column 1 line 10-column 3 line 30, column 9 line 53- column 11 line 19, column 18 line 16 – column 25 line 55 and claims 8-21, 25-31).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings above to claim the methods as in the instant application. All of the moieties and locations of substitution are taught in the art as discussed above as well as the methods of treatment claimed by the applicant. Obviousness based on the significant similarity

of structure and function entails the motivation to claim the same methods for the same compounds in expectation that similar compounds will have similar properties. Therefore, one of ordinary skill in the art would be motivated to claim methods taught in the prior art when claiming those very compounds as disclosed in the prior art.

The applicant may obviate this rejection by amending the claims to exclude the prior art, canceling the claims or amending the claims to include a proviso wherein the methods relating to the compounds and compositions claimed will not be obvious over the prior art. If the applicant chooses anyone of the methods above to obviate the rejection then the applicant is encouraged to include a brief and concise explanation of how the amendments obviate the rejection from the prior art in order to expedite prosecution.

Claim Rejections - 35 USC § 112 First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 16 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for activity against kinases such as CDK, EMT, FAK, Her1, Her2, IGF IR, LCK, MET, PDGF, VEGF, HT-29 and Colo25, does not reasonably provide enablement for a method of treating all cancers and all proliferative diseases or all conditions associated with at least one tyrosine kinase enzyme. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 13, 16 and 18 are directed to a method of treating cancer and proliferative diseases and conditions associated with at least one tyrosine enzyme. The term cancer is interpreted to include any and all forms of cancer that are characterized as any malignant growth or tumor caused by abnormal and uncontrolled cell division that may spread to other parts of the body through the lymphatic system or the blood stream. The phrase proliferative disease is interpreted to include any disease that that grows or multiplies by rapidly producing new tissue, parts, cells, or offspring or to increase or spread at a rapid rate such as solid and metastasized tumors.

In light of this, it can be asserted that in spite of the vast expenditure of human and capital resources in recent years, no one drug has been found which is effective in treating all types of cancer or proliferative diseases because it is not a simple disease, nor is it even a single disease, but a complex of a multitude of different entities, each behaving in a different way. In re Hozumi, 226 USPQ 353 (ComrPats 1985).

Moreover, the determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the factual considerations. In re Wands, 8 USPQ2d 1400 (CAFC). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include but are not limited to:

1. The breadth of the claims;

2. The nature of the invention;

3. The state of the prior art;

4. The level of one of ordinary skill;

5. The level of predictability in the art;

6. The amount of direction provided by the inventor;

7. The existence of working examples; and

8. The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Wands Analysis

1. The Breadth of the Claims.

The breadth of the instant claims are seen to encompass the treatment of all forms of cancer and proliferative diseases that are characterized as any malignant growth or tumor caused by abnormal and uncontrolled cell division that may spread to other parts of the body through the lymphatic system or the blood stream or any disease that that grows or multiplies by rapidly producing new tissue, parts, cells, or offspring or to increase or spread at a rapid rate such as solid and metastasized tumors. In addition, the breadth of the instant claims are seen to include treating conditions associated with at least one tyrosine kinase enzyme which encompasses treating cancer broadly, by administering compounds of claim 1. Moreover, the claims are seen to encompass all proliferative disease, in the absence of some specific delineation of the proliferative diseases intended in claim 18

2. The Nature of the Invention.

The nature of the invention is the treatment of cancer and proliferative diseases through the use of the claimed compounds, compositions and derivatives thereof. Currently, there are no known agents that treat cancers all inclusively.

The nature of the invention is further seen to be the treatment of conditions associated with the activity of the tyrosine kinase enzyme. This loose association is not seen to provide substantive data or information to provide treatment of disorders or diseases associated with said enzyme. Disorders and diseases could be associated tangentially with the asserted enzyme activity. There is not seen sufficient evidence or data to substantiate the asserted usefulness of the instant claims to affect conditions "associated" with one or more tyrosine kinase enzymes.

3. The State of the Prior Art.

The applicant has submitted data in the specification wherein the claimed compounds found in the specification examples have shown activity against kinases such as CDK, EMT, FAK, Her1, Her2, IGF IR, LCK, MET, PDGF, VEGF, HT-29 and Colo25. However, the applicant has not submitted data, evidence or references in the prior art showing that the claimed compounds are efficacious against an adequate representation of the known forms of cancer and proliferative diseases. Furthermore, the prior art does not teach that compounds of the class claimed are effective against all forms or cancer and proliferative diseases.

4. The Level of Ordinary Skill

The level of skill is that of one with a doctoral understanding of cancer therapeutics.

5. The Level of Predictability in the Art

The treatment of conditions associated with one or more tyrosine kinase enzymes, wherein the association is not specifically set forth, or the conditions specified as cancer or proliferative diseases are highly unpredictable. Without knowing the association between the enzymes and all conditions to be treated, one skilled in chemotherapy would not be able to predict what conditions to use the claimed compounds upon. Furthermore, the treatment of cancer is unpredictable due to the differing forms of cancerous cells, their location, their potential for metastases, the fact that cancer therapeutics is palliative rather than curative and that cancer treatment readily harms normal tissues (see Katzung pp. 881-882).

6. The Amount of Direction Provided by the Inventor

The applicant has not demonstrated sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or reference to the same in the prior art to provide a skilled artisan with sufficient guidance to practice the instant treatment of conditions associated with one or more tyrosine kinase enzymes. For example, the applicant only discloses that dosages should be an effective amount without providing a dosage or range of dosages from which the dosage may be adjusted to treat all cancers and proliferative diseases.

7. The Existence of Working Examples

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 27 USPQ2d 1510 (CAFC). The disclosure does not demonstrate sufficient evidence to support the applicant's claim to the treatment of cancer and

proliferative diseases. There are not sufficient working examples, adequate representations in the disclosure or data from references of the prior art to provide a nexus between those examples and a method of treating cancer and proliferative diseases with the claimed compounds and compositions.

8. The Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure

In order for there to be a method of treating cancer and proliferative diseases generally, as claimed by the applicant, it would be necessary to show that a vast range of different types of cancers and proliferative diseases can be treated that have differing cell types, locations and potentials for metastases. Furthermore, direction, in the form of examples, must be shown to determine what an effective dose may be. The references submitted do not demonstrate this. Therefore, one of ordinary skill in the art would require a significant amount of experimentation in order to determine the effective dosage to treat the multitudes of different types of cancer with the claimed compound individually or in combination with other therapeutic agents (See Katzung pp. 882-884).

Claim Rejections - 35 USC § 112 Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 13-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13 and 17 use the phrase "an effective amount" and "therapeutically effective amount" without providing any guidance to what an effective amount may be or how and effective amount may be calculated. For purposes of examination, the phrase "an effective amount" will be construed to mean any amount.

Claim 16 uses the term "cancer" without defining what type of cancer to be treated. For purposes of examination the term cancer will be interpreted to mean any malignant growth or tumor caused by abnormal and uncontrolled cell division that may spread to other parts of the body through the lymphatic system or the blood stream.

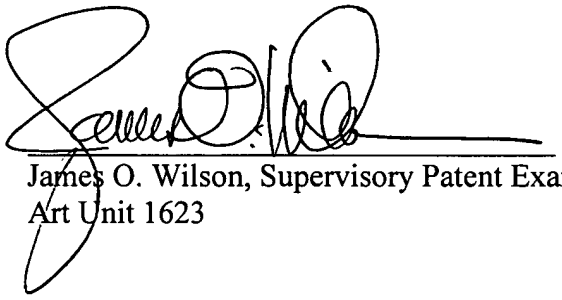
Claim 18 uses the phrase "proliferative diseases" without defining what those proliferative disease are. The term "proliferative" is defined as meaning to grow or multiply by rapidly producing new tissue, parts, cells, or offspring or to increase or spread at a rapid rate. This could mean a myriad of diseases that proliferate such as bacterial infections, solid and metastasized tumors as well as viral infections to name a few. For purposes of examination, the phrase "proliferative diseases" will be interpreted as any disease that grows or multiplies by rapidly producing new tissue, parts, cells, or offspring or to increase or spread at a rapid rate.

Claims 14 and 15 are also rejected as being indefinite since they depend from indefinite base claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew L. Fedowitz whose telephone number is (571) 272-3105. If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, James O. Wilson, can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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Art Unit 1623